

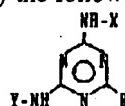
**(57). (Abstract).**

**Object**

To put forward a novel application of 2,4-diamino-1,3,5-triazine derivatives.

**Construction**

Leukotriene antagonist of this invention is characterised in containing as effective component a compound represented by the following formula:



(in the formula, X and Y denotes hydrogen atom or acyl group, R denotes a substituted or unsubstituted phenyl group, or phthalidylmethyl group, or substituted or unsubstituted 2-arylethenyl group or the like).

**Effect**

In accordance with this invention, leukotriene antagonist containing as effective component 2,4-diamino-1,3,5-triazine derivative is put forward.

**Patent Claims**

**Claim 1**

A leukotriene antagonist containing as effective component 2,4-diamino-1,3,5-triazine derivatives represented by the following formula (1) or pharmaceutically acceptable salt thereof



[In the formula, X and Y may be the same or different and denote hydrogen atom or acyl group; R denotes substituted or unsubstituted phenyl group or phthalidylmethyl group, or a group represented by the following formula (2)

-A-R1 (2)

(in the formula, A denotes -CH<sub>2</sub>-CH<sub>2</sub>- or -CH=CH-; R1 denotes a substituted or unsubstituted phenyl group, naphthyl group or pyridyl group)].

**Detailed Description of the Invention**

**(0001)**

**Technical Sphere of the Invention.**

This invention relates to a leukotriene antagonist useful as therapeutic or preventive

agent of allergic diseases, inflammatory diseases, cardiovascular disorder or the like.

**(0002)**

Technology of the Prior Art.

As far as leukotriene is concerned, its biological significance has been widely researched, and in particular the significance thereof has been reported in various diseases such as neonatal anoxia, pulmonary circulation hypertension, adult respiratory distress syndrome, psoriasis, spondylarthritis, rheumatoid arthritis, gout, inflammatory enteritis or the like, and the leukotriene antagonist that displays antagonism to leukotriene is useful as therapeutic or preventive agent of allergic diseases, inflammatory diseases, cardiovascular disorder or the like.

**(0003)**

On the other hand, as far as 2,4-diamino-1,3,5-triazine derivatives, an application as antiulcerative agent has been reported (Kokai 2-223566, Kokoku 55-4751), however, there is no report whatsoever about the action on leukotriene.

**(0004)**

Problems to be Overcome by this Invention

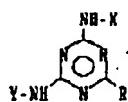
This invention has an object of putting forward a novel application of 2,4-diamino-1,3,5-triazine derivatives.

**(0005)**

Means to Overcome these Problems

The leukotriene antagonist of this invention is characterised in containing as effective component 2,4-diamino-1,3,5-triazine derivatives represented by the following formula (1) or pharmaceutically acceptable salt thereof

**(0006)**



(1)

(0007)

[In the formula, X and Y may be the same or different and denote hydrogen atom or acyl group; R denotes a substituted or unsubstituted phenyl group or phthalidylmethyl group, or a group represented by the following formula (2)

-A-R1 (2)

(in the formula, A denotes -CH<sub>2</sub>-CH<sub>2</sub>- or -CH=CH-; R<sub>1</sub> denotes a substituted or unsubstituted phenyl group, naphthyl group or pyridyl group]).

(0008)

As the acyl group represented by X or Y in the aforesaid formula (1), for example, acetyl group, substituted or unsubstituted nicotinoyl group or benzoyl group or the like can be nominated. Moreover, the phenyl group or phthalidylmethyl group represented by R may be unsubstituted or substituted with suitable substituents. As such suitable substituents, for example, halogen atom, hydroxy group, lower alkyl group, lower alkoxy group, lower alkoxy carbonyl group, lower alkoxy- lower alkoxy group, trifluoromethyl group or the like can be nominated.

(0009)

Moreover, the phenyl group naphthyl group or pyridyl group represented by R1 may be unsubstituted or substituted with suitable substituents. As such suitable substituents, for example, halogen atom, hydroxy group, cyano group, lower alkyl group, lower alkoxy group, lower alkoxy carbonyl group, lower alkoxy- lower alkoxy group, trifluoromethyl group, phenyl group, phenoxy group, benzyl group, benzyloxy group, or phenoxy group substituted with trifluoromethyl group or lower alkyl group or the like can be nominated.

(0010)

In this specification, halogen atom denotes chlorine atom, fluorine atom, bromine atom or the like; lower alkyl group denotes alkyl group of carbon number 1-6, for example, methyl group, ethyl group, propyl group, isopropyl group, butyl group, tert-butyl, sec-butyl group, pentyl group, hexyl group or the like; lower alkoxy group denotes alkoxy group of carbon number 1-6, for example, methoxy group, ethoxy group, propoxy group or the like; lower alkoxycarbonyl group denotes alkoxycarbonyl group of carbon number 1-6, for example, methoxycarbonyl group, ethoxycarbonyl group or the like; lower alkoxy-lower alkoxy group denotes alkoxy-alkoxy group of carbon number 1-6, for example, methoxymethoxy group or the like.

(0011)

Among the compounds represented by the aforesaid formula (1), the compounds in which R is -CH=CH-R<sub>1</sub>, namely, compounds represented by the following formula (3):

(0012)



(0013)

can be produced by condensation of a compound represented by the following formula (4):

(0014)



(0015)

with an aldehyde compound represented by R<sub>1</sub>-CHO in the presence of acid or base. As the acid, for example, methanesulphonic acid, formic acid, sulphuric acid can be nominated, and as the base, for example, potassium hydroxide, sodium hydroxide, Triton B, sodium methoxide or the like can be nominated. When an acid is used, the reaction is usually carried out without solvent, however, when a base is used, solvent such as methanol, ethanol, 2-methoxyethanol is used. The reaction temperature is preferably 60-120°C, the reaction time is 1 hour to 7 days.

(0016)

Among the compounds represented by the aforesaid formula (1), the compounds in which R is -CH<sub>2</sub>CH<sub>2</sub>-R<sub>1</sub> can be produced by reducing the aforesaid compound (3) by conventional process. Among the compounds represented by the aforesaid formula (1), the compounds in which X and/or Y is acyl group can be produced by reacting the compound represented by the following formula (5):

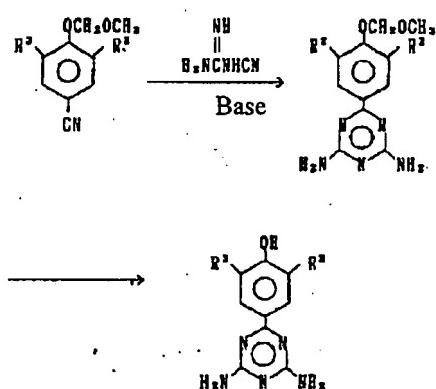
(0017)



## (0018)

with a corresponding acid chloride or acid anhydride in pyridine. The reaction temperature is 80-140°C, preferably 110-120°C, the reaction time is usually 3-8 hours. Among the compounds represented by the aforesaid formula (1), the compounds in which R is substituted or unsubstituted phenyl group can be produced by reacting corresponding benzonitrile derivative and dicyandiamide in the presence of base in accordance with the process of Kokoku 55-4751. During this, when R is hydroxy-substituted phenyl group, a process as illustrated below is preferably used wherein the hydroxy group is protected in the form of methoxymethoxy group, cyclisation is caused, this is treated with acid, thereby it is converted to hydroxy group.

## (0019)

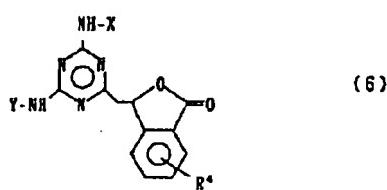


## (0020)

(in the formula, R<sub>2</sub> and R<sub>3</sub> denote for example lower alkyl group)

Among the compounds represented by aforesaid formula (1), compounds in which R is substituted or unsubstituted phthalidymethyl group, namely compounds represented by the following formula (6):

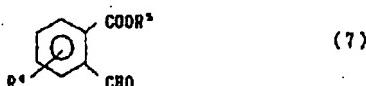
## (0021)



(0022)

(in the formula, R4 denotes hydrogen atom or suitable substituents ) can be produced by reacting the aforesaid compound (4) with a compound represented by the following formula (7):

(0023)



(0024)

(in the formula, R5 denotes hydrogen atom or lower alkyl group) in the presence of acid.

Moreover, a compound represented by the following formula (8):

(0025)



(0026)

and an acid chloride represented by the following formula (9):

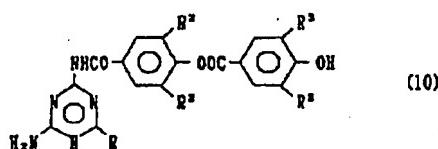
(0027)



(0028)

(in the formula, R2 and R3 have the same said meanings) are reacted, and thereby compounds in which either one of X or Y is substituted or unsubstituted 4-(4-hydroxybenzoyloxy) benzoyl group and the other is hydrogen atom among the compounds represented by aforesaid formula (1), namely compounds represented by the following formula (10):

(0029)



(0030)

can be produced.

The leukotriene antagonist of this invention contains as effective component a compound represented by aforesaid formula (1) or pharmaceutically acceptable salt thereof, for example, hydrochloride, maleate, fumarate, and is useful as therapeutic or preventive agent of allergic diseases, inflammatory diseases, cardiovascular disorder or the like.

**(0031)**

Next, administration and pharmaceutical formulation of the leukotriene antagonist of this invention will be explained. The compound of general formula (1) can be administered as it is or together with conventional pharmaceutical carrier to animals or humans. The administration forms are not limited in particular, and can be suitably selected in accordance with requirements, and oral agents such as tablets, capsules, granules, fine granules, powder or the like, parenteral agents such as injection, suppository or the like can be nominated.

**(0032)**

In order to display the desired effect as an oral agent, although the quantity differs depending on the age of the patient, severity of disease, but usually for an adult, the compound of general formula (1) 0.2-25 mg/kg body wt is preferably administered once or several times per day. The compound of general formula (1) which is the effective component of leukotriene antagonist of this invention can be formulated into preparation such as liquid agent, powder, granules tablet, enteric coated agent, capsule or the like in accordance with conventional agent production method using suitable solvent, excipient, adjuvant or the like used for the preparation, and this can be orally or parenterally administered.

**(0033)**

For the prescription, combined agent with other medically active component can be formed. For the purpose of oral administration, table, pill, capsule, powder granules or the like can be prescribed using at least one type of excipient, for example, starch, lactose, sucrose, mannitol, carboxymethyl cellulose or the like. In this type of agent, in addition to aforesaid excipient, for example, lubricant such as magnesium stearate, sodium laurylsulphate, talc or the like, binder such as dextrin, crystalline cellulose, polyvinylpyrrolidone, gum Arabic, corn starch, gelatine or the like, disintegration agent such as sodium carboxy cellulose, potato starch, carboxymethyl cellulose or the like, fluidity promoter such as light anhydrous silicic acid can be suitably used. Moreover, the leukotriene antagonist of this invention can be administered as suspension, emulsion, syrup, elixir, and these agents may contain corrigent filler and colouring agent.

(0034)

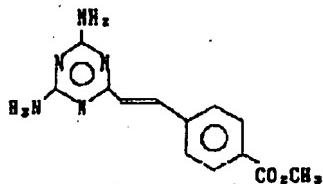
**Examples**

Below this invention is explained in greater detail with Synthesis Examples, Examples, Test Examples and Preparation Examples, however, the scope of this invention is not limited to these.

**Synthesis Example 1**

2,4-diamino-[E]-6-[2-(4-methoxycarbonylphenyl) ethenyl]-1,3,5-triazine (compound 18)

(0035)



(0036)

2,4-diamino-6-methyl-1,3,5-triazine 5 g (40 mM) was dissolved in 50 ml formic acid, thereto was added 6.56 g (40 mM) 4-formylbenzoic acid methyl ester, and the mixture was heated under reflux for 91 hours. The reaction liquor was concentrated under reduced pressure, thereafter, was made alkaline with addition of saturated sodium hydrogen carbonate, the precipitated crystals were recovered with filtration, washed with water, thereafter, re-crystallised from a mixed solvent of 2-methoxyethanol and ethanol, and thereby the title compound (4.58 g 42.3 %) was obtained.

Melting point: 258°C (Decomposition)

1H-NMR (200 MHz) δ (DMSO-d6): 3.87 (3H, s), 6.67 (4H, br s), 6.86 (1H, d, J = 15.9 Hz), 7.76 (2H, d, J = 8.5 Hz), 7.82 (1H, d, J = 15.9 Hz), 7.97 (2H, d, J = 8.5 Hz).

MS m/z (%) [EI]: 271 (M+, 65), 270 (100), 228 (37), 128 (21).

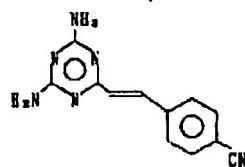
**Synthesis Example 2 and 3**

The following compounds were synthesised by the same method as in Synthesis Example 1.

**Synthesis Example 2**

2,4-diamino-[E]-6-[2-(4-cyanophenyl) ethenyl]-1,3,5-triazine (compound 19)

(0037)



(0038)

Yield: 17.9 %

Melting point: >300°C (from 2-methoxyethanol)

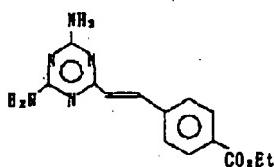
1H-NMR (200 MHz) δ (DMSO-d6): 6.70 (4H, br s), 6.90 (1H, d, J = 15.9 Hz), 7.80 (1H, d, J = 15.9 Hz), 7.83 (4H, s).

MS m/z (%) [EI]: 283 (M+, 75), 237 (100), 195 (41), 169 (25).

#### Synthesis Example 3

2,4-diamino-[E]-6-[2-(4-ethoxycarbonylphenyl)ethenyl]-1,3,5-triazine (compound 22)

(0039)



(0040)

Yield: 15.0 %

Melting point: 229.6-230.8°C (from ethanol)

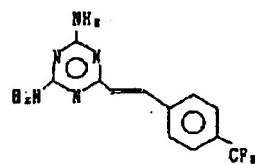
1H-NMR (200 MHz) δ (DMSO-d6): 1.34 (3H, t, J = 7.1 Hz), 4.33 (2H, q, J = 7.1 Hz), 6.68 (4H, br s), 6.87 (1H, d, J = 16.1 Hz), 7.76 (2H, d, J = 8.3 Hz), 7.82 (1H, d, J = 16.1 Hz), 7.97 (2H, d, J = 8.3 Hz).

MS m/z (%) [EI]: 285 (M+, 74), 284 (100), 256 (25), 242 (22).

#### Synthesis Example 4

2,4-diamino-[E]-6-[2-(4-trifluoromethylphenyl)ethenyl]-1,3,5-triazine (compound 20)

(0041)



(0042)

2,4-diamino-6-methyl-1,3,5-triazine 5 g (40 mM) was dissolved in 28 ml methane sulphonic acid, thereto was added 5.5 ml (40 mM) 4-trifluoromethylbenzaldehyde, and the mixture was stirred at 110 °C for 2 hours. After cooling, dilute aqueous sodium hydroxide was added to the reaction liquor to make it alkaline, and the precipitated crystals were recovered by filtration and washed with water, and thereafter, recrystallised from ethanol, and thereby the title compound (6.09 g, 54.2 %) was obtained.

Melting point: 274.9-275.7°C.

1H-NMR (200 MHz) δ (DMSO-d<sub>6</sub>): 6.70 (4H, br s), 6.88 (1H, d, J = 15.9 Hz), 7.73 (2H, d, J = 8.3 Hz), 7.83 (1H, d, J = 15.9 Hz), 7.85 (2H, d, J = 8.3 Hz).

MS m/z (%) [EI]: 281 (M<sup>+</sup>, 93), 280 (100), 238 (54), 212 (28), 196 (22), 111 (26).

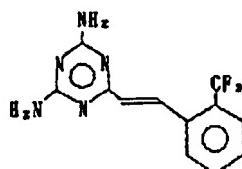
### Synthesis examples 5-13

The following compounds were synthesised by the same method as in Synthesis Example 4.

### Synthesis Example 5

2,4-diamino-[E]-6-[2-(2-trifluoromethylphenyl) ethenyl]-1,3,5-triazine (compound 21)

(0043)



0044)

Yield: 54.0 %

Melting point: 250.0-250.9°C (from ethanol).

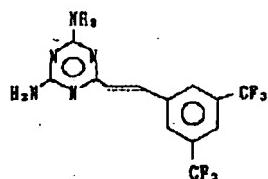
1H-NMR (200 MHz) δ (DMSO-d<sub>6</sub>): 6.72 (4H, br s), 6.78 (1H, d, J = 15.9 Hz), 7.50-8.10 (4H, m), 8.11 (1H, brd, J = 15.9 Hz).

MS m/z (%) [EI]: 281 (M<sup>+</sup>, 100), 212 (76), 170 (53), 111 (32).

### Synthesis Example 6

2,4-diamino-[E]-6-[2-{3,5-bis(trifluoromethyl)phenyl} ethenyl]-1,3,5-triazine  
(compound 24)

(0045)



(0046)

Yield: 50.6 %

Melting point: 208.2-209.0°C (from ethanol).

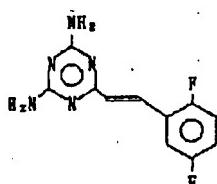
1H-NMR (200 MZ) δ (DMSO-d6): 6.68 (4H, br s), 7.08 (1H, d, J = 15.9 Hz), 7.89 (1H, d, J = 15.9 Hz), 8.00 (1H, br s), 8.33 (2H, br s).

MS m/z (%) [EI]: 349 (M+, 100), 348 (56), 330 (22), 280 (27) 111 (60).

#### Synthesis Example 7

2,4-diamino-[E]-6-[2-(2,5-difluorophenyl) ethenyl]-1,3,5-triazine (compound 25)

(0047)



(0048)

Melting point: >300°C (from 2-methoxyethanol).

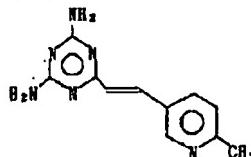
1H-NMR (200 MZ) δ (DMSO-d6): 6.71 (4H, br s), 6.89 (1H, d, J = 16.1 Hz), 7.20-7.40 (2H, m), 7.70-7.80 (1H, m), 7.90 (1H, br d, J = 16.1 Hz).

MS m/z (%) [EI]: 249 (M+, 57), 228 (100), 188 (29), 146 (20).

#### Synthesis Example 8

2,4-diamino-[E]-6-[2-(6-methylpyridin-3-yl) ethenyl]-1,3,5-triazine (compound 26)

(0049)



(0050)

Yield: 36.6 %

Melting point: 253.7-254.3°C (from ethanol).

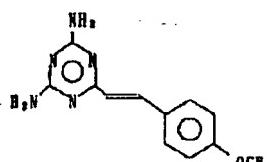
1H-NMR (200 MZ) δ (DMSO-d6): 2.49 (3H, s), 6.66 (4H, br s), 6.80 (1H, d, J = 15.9 Hz), 7.28 (1H, d, J = 8.3 Hz), 7.77 (1H, d, J = 15.9 Hz), 7.99 (1H, dd, J = 8.3, 2.2 Hz),

8.63 (1H, d,  $J = 2.2$  Hz).

MS m/z (%) [EI]: 228 (M+, 45), 227 (100), 185 (37), 144 (23).

### Synthesis Example 9

2,4-diamino-[E]-6-[2-(4-methoxyphenyl) ethenyl]-1,3,5-triazine (compound 32) (0051)



(0052)

Yield: 27.4 %

Melting point: 244°C (decomposition) (from ethanol).

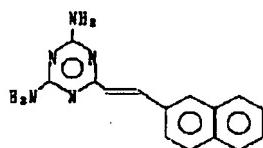
<sup>1</sup>H-NMR (200 MHz) δ (DMSO-d<sub>6</sub>): 3.79 (3H, s), 6.59 (4H, br s), 6.59 (1H, d, J = 15.9 Hz), 6.96 (2H, d, J = 8.8 Hz), 7.56 (2H, d, J = 8.8 Hz), 7.75 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 243 (M+, 88), 242 (100), 200 (32), 158 (19).

### Synthesis Example 10

2,4-diamino-[E]-6-[2-(2-naphthyl) ethenyl]-1,3,5-triazine (compound 33)

(0053)



(0054)

Melting point: 237.8-238.4°C (from methanol).

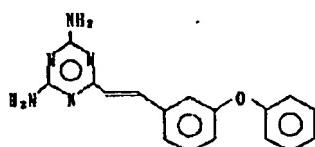
<sup>1</sup>H-NMR (200 MHz) δ (DMSO-d<sub>6</sub>): 6.82 (4H, br s), 6.93 (1H, d, J = 15.9 Hz), 7.50-7.70 (2H, m), 7.80-8.20 (5H, m), 8.02 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 263 (M+, 100), 262 (96), 220 (44), 179 (21) 178 (36).

### Synthesis Example 11

2,4-diamino-[E]-6-[2-(3-phenoxyphenyl) ethenyl]-1,3,5-triazine (compound 34)

(0055)



(0056)

Melting point: 167.6-169.4°C (from methanol).

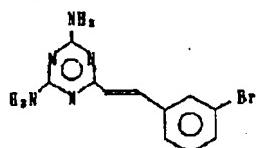
1H-NMR (200 MHz) δ (DMSO-d<sub>6</sub>): 6.64 (4H, br s), 6.68 (1H, d, J = 15.9 Hz), 6.90-7.50 (9H, m), 7.73 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 305 (M<sup>+</sup>, 87), 304 (100), 262 (29), 220 (23).

### Synthesis Example 12

2,4-diamino-[E]-6-[2-(3-bromophenyl) ethenyl]-1,3,5-triazine (compound 35)

(0057)



(0058)

Yield: 59.9 %

Melting point: 188.9-189.7°C (from methanol-2-methoxyethanol).

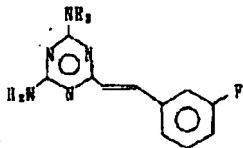
1H-NMR (200 MHz) δ (DMSO-d<sub>6</sub>): 6.66 (4H, br s), 6.79 (1H, d, J = 15.9 Hz), 7.36 (1H, dd, J = 7.8, 7.8 Hz), 7.54 (1H, br d, J = 7.8 Hz), 7.63 (1H, br d, J = 7.8 Hz), 7.72 (1H, d, J = 15.9 Hz), 7.82 (1H, br s).

MS m/z (%) [EI]: 293 (M<sup>+</sup>, 77), 292 (100), 291 (M<sup>+</sup>, 76), 290 (93), 250 (29), 248 (28) 128 (40).

### Synthesis Example 13

2,4-diamino-[E]-6-[2-(3-fluorophenyl) ethenyl]-1,3,5-triazine (compound 36)

(0059)



(0060)

Melting point: 275.9-276.8°C (from methanol-2-methoxyethanol).

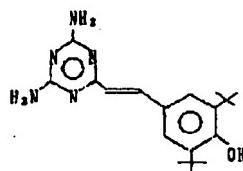
1H-NMR (200 MHz) δ (DMSO-d<sub>6</sub>): 6.69 (4H, br s), 6.80 (1H, d, J = 15.9 Hz), 7.10-7.25 (1H, m), 7.30-7.55 (3H, m), 7.76 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 231 (M<sup>+</sup>, 76), 230 (100), 188 (45), 162 (28), 146 (22).

### Synthesis Example 14

2,4-diamino-[E]-6-[2-(3,5-di-t-butyl-4-hydroxyphenyl) ethenyl]-1,3,5-triazine

(compound 37)  
(0061)



(0062)

2,4-diamino-6-methyl-1,3,5-triazine 2.5 g (20 mM) was dissolved in 75 ml formic acid, thereto was added 5.15 g (22 mM) 3,5-di-t-butyl-4-hydroxybenzaldehyde, and the mixture was heated under reflux for 168 hours. The reaction liquor was concentrated under reduced pressure, and the obtained residue was purified by silica gel flash chromatography (CHCl<sub>3</sub> : MeOH = 9 : 1), and thereafter, re-crystallised from 2-propanol, and the title compound (0.85 g, 12.5 %) was obtained.

Melting point: 253.3-255.7°C.

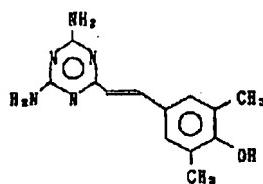
<sup>1</sup>H-NMR (200 MHz) δ (CD<sub>3</sub>OD): 1.45 (18H, s), 6.59 (1H, d, J = 15.9 Hz), 7.41 (2H, s), 7.85 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 342 (M++1, 24), 341 (M+, 99), 327 (23), 326 (100), 270 (18).

#### Synthesis example 15

2,4-diamino-[E]-6-[2-(4-hydroxy-3,5-dimethylphenyl) ethenyl]-1,3,5-triazine (compound 49)

(0063)



(0064)

The title compound was synthesised by the same method as in Synthesis Example 14.

Yield: 18.7 %

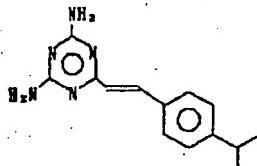
Melting point: 285.9-288.1°C (decomposition) (from 2-propanol-methanol).

<sup>1</sup>H-NMR (200 MHz) δ (DMSO-d<sub>6</sub>): 2.19 (6H, s), 6.50 (1H, d, J = 15.9 Hz), 6.55 (4H, br s), 7.17 (2H, s), 7.66 (1H, d, J = 15.9 Hz), 8.12 (1H, s).

MS m/z (%) [EI]: 257 (M+, 100), 256 (70), 214 (25).

#### Synthesis Example 16

2,4-diamino-[E]-6-[2-(4-isopropylphenyl) ethenyl]-1,3,5-triazine (compound 41)  
**(0065)**



(0066)

2,4-diamino-6-methyl-1,3,5-triazine 1.25 g (10 mM) was dissolved in 20 ml 2-methoxyethanol, thereto were added 9.1 ml (20 mM) Triton B (40% methanol solution) and 3 ml (19.8 mM) 4-isopropylbenzaldehyde, and the mixture was stirred at 80 °C for 6.5 hours. After cooling, water was added and the precipitated crystals were collected by filtration and washed with water, and thereafter re-crystallised from the mixed solvent of 2-methoxyethanol and methanol, and the title compound (0.91 g, 35.7 %) was obtained. Melting point: 247.8-248.8°C.

Melting point: 247.8-248.8°C.

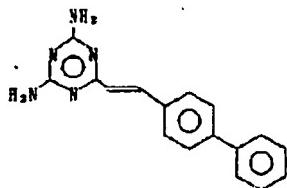
<sup>1</sup>H-NMR (200 MHz) δ (DMSO-d<sub>6</sub>): 1.21 (6H, d, J = 6.8 Hz), 2.91 (1H, m), 6.62 (4H, br s), 6.68 (1H, d, J = 16.1 Hz), 7.27 (2H, d, J = 8.1 Hz), 7.53 (2H, d, J = 8.1 Hz), 7.77 (1H, d, J = 16.1 Hz).

MS m/z (%) [EI]: 255 (M+, 53), 254 (100), 240 (18), 212 (19), 156 (16).

### Synthesis Example 17

2,4-diamino-[E]-6-[2-(4-biphenyl) ethenyl]-1,3,5-triazine (compound 42)

(0067)



(0068)

2,4-diamino-6-methyl-1,3,5-triazine 1.25 g (10 mM) was dissolved in 30 ml 2-methoxyethanol, thereto were added 0.66 g (10 mM) potassium hydroxide (85%) and 2.91 g (16 mM) 4-biphenylcarboxaldehyde, and the mixture was stirred at 90 °C for 16 hours. After cooling, water was added and the precipitated crystals were collected by filtration and washed with water, and thereafter, re-crystallised from the mixed solvent of 2-methoxyethanol and methanol, and the title compound (0.60 g; 20.7%) was obtained.

Melting point: 276°C (decomposition)

<sup>1</sup>H-NMR (200 MHz) δ (DMSO-d<sub>6</sub>): 6.66 (4H, br s), 6.79 (1H, d, J = 15.9 Hz), 7.35-7.75

(5H, m), 7.72 (4H, s), 7.84 (1H, d, J = 15.9 Hz).

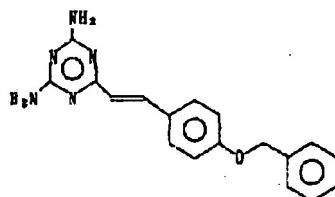
MS m/z (%) [EI]: 289 (M+, 82), 288 (100), 246 (34), 220 (13), 205 (16), 204 (31).

### Synthesis examples 18-22

The following compounds were synthesised by the same method as in Synthesis Example 17.

#### Synthesis example 18

2,4-diamino-[E]-6-[2-(4-benzyloxyphenyl) ethenyl]-1,3,5-triazine (compound 44)  
(0069)



(0070)

Yield: 16.6 %

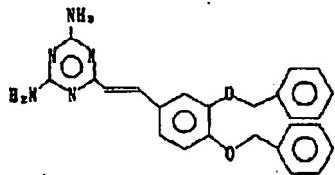
Melting point: 227.2-227.9°C (from methanol-2-methoxyethanol).

1H-NMR (200 MHz) δ (DMSO-d6): 5.15 (2H, s), 6.58 (4H, br s), 6.59 (1H, d, J = 15.9 Hz), 7.03 (2H, d, J = 8.8 Hz), 7.30-7.50 (5H, m), 7.56 (2H, d, J = 8.8 Hz), 7.74 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 319 (M+, 11), 228 (39), 91 (100), 78 (22).

#### Synthesis example 19

2,4-diamino-[E]-6-[2-(3,4-bis(benzyloxy) phenyl) ethenyl]-1,3,5-triazine (compound 45)  
(0071)



(0072)

Yield: 54.6 %

Melting point: 203.2-203.7°C (from methanol-2-methoxyethanol).

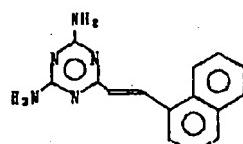
1H-NMR (200 MHz) δ (DMSO-d6): 5.18 (2H, s), 5.22 (2H, s), 6.56 (4H, br s), 6.61 (1H, d, J = 15.9 Hz), 7.00-7.15 (2H, m), 7.25-7.55 (11H, m), 7.69 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 425 (M+, 5), 334 (17), 91 (100).

### Synthesis example 20

2,4-diamino-[E]-6-[2-(1-naphthyl) ethenyl]-1,3,5-triazine (compound 46)

(0073)



(0074)

**Yield: 27.8 %**

Melting point: 220.1-221.2°C (from 2-methoxyethanol-methanol-ethyl acetate).

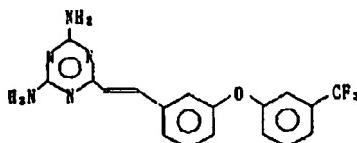
<sup>1</sup>H-NMR (200 MHz) δ (DMSO-d<sub>6</sub>): 6.72 (4H, br s), 6.81 (1H, d, J = 15.9 Hz), 7.50-7.70 (3H, m), 7.90-8.05 (3H, m), 8.18 (1H, br d, J = 7.8 Hz), 8.64 (1H, d, J = 15.9 Hz).

MS m/z (%) [EI]: 263 (M+, 100), 262 (68), 220 (22), 178 (28).

### Synthesis example 21

2,4-diamino-[E]-6-[2-{3-(3-trifluoromethylphenoxy) phenyl} ethenyl]-1,3,5-triazine  
(compound 47)

(0075)



(0076)

**Yield: 42.6 %**

Melting point: 204.7-205.8°C (from ethanol-2-methoxyethanol).

<sup>1</sup>H-NMR (200 MHz) δ (DMSO-d<sub>6</sub>): 6.63 (4H, br s), 6.72 (1H, d, J = 15.9 Hz), 7.00-7.70 (8H, m), 7.76 (1H, d, J = 15.9 Hz).

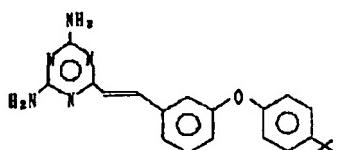
MS m/z (%) [EI]: 374 (M++1, 92), 373 (M+, 100), 330 (34), 289 (15), 112 (12).

### Synthesis example 22

2,4-diamino-[E]-6-[2-{3-(4-t-butylphenoxy) phenyl} ethenyl]-1,3,5-triazine (compound

48)

(0077)



(0078)

Yield: 34.9 %

Melting point: 211.6-212.2°C (from ethanol).

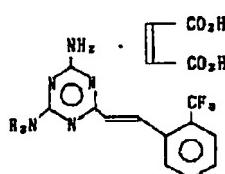
$^1\text{H-NMR}$  (200 MZ)  $\delta$  (DMSO-d6): 1.30 (9H, s), 6.64 (4H, br s), 6.69 (1H, d,  $J = 15.9$  Hz), 6.90-7.00 (3H, m), 7.20 (1H, br s), 7.30-7.50 (4H, m), 7.73 (1H, d,  $J = 15.9$  Hz).

MS m/z (%) [EI]: 361 (M+, 64), 360 (38), 347 (25), 346 (100).

### Synthesis example 23

2,4-diamino-[E]-6-[2-(2-trifluoromethylphenyl) ethenyl]-1,3,5-triazine maleate (maleate of compound 21 (the compound of synthesis example 5))

(0079)



(0080)

0.5 g (1.77 mM) compound 21 was dissolved in 50 ml ethanol, thereto was added 0.25 g (2.15 mM) maleic acid, and the mixture was left to stand at room temperature for 0.5 hours. The precipitated crystals were collected by filtration and washed with ethanol, and the title compound (0.60 g, 85.7 %) was obtained.

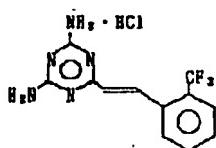
Melting point: 195.6-196.2°C (decomposition) (from ethanol).

$^1\text{H-NMR}$  (200 MZ)  $\delta$  (DMSO-d6): 6.21 (2H, s), 6.83 (1H, d,  $J = 15.9$  Hz), 7.06 (4H, br s), 7.55-7.85 (3H, m), 7.99 (1H, d,  $J = 7.6$  Hz), 8.15 (1H, brd,  $J = 15.6$  Hz).

### Synthesis example 24

2,4-diamino-[E]-6-[2-(2-trifluoromethylphenyl) ethenyl]-1,3,5-triazine hydrochloride (hydrochloride of compound 21 (the compound of synthesis example 5))

(0081)



(0082)

0.5 g (1.77 mM) compound 21 was dissolved in 50 ml ethanol, thereto was added 0.3 g concentrated hydrochoric acid, and the mixture was left to stand at room temperature for 0.5 hours. The precipitated crystals were collected by filtration and washed with ethanol, and the title compound (0.38 g, 67.9 %) was obtained.

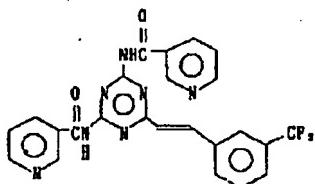
Melting point: >300°C (from ethanol).

1H-NMR (200 MHz) δ (DMSO-d6): 7.01 (1H, d, J = 15.6 Hz), 7.60-7.90 (3H, m), 7.99 (1H, d, J = 7.6 Hz), 8.00-8.60 (4H, br), 8.29 (1H, br d, J = 15.6 Hz).

#### Synthesis Example 25

2,4-bis (nicotinoylamino)-[E]-6-[2-(3-trifluoromethylphenyl) ethenyl]-1,3,5-triazine (compound 23)

(0083)



(0084)

1 g (3.55 mM) 2,4-diamino-[E]-6-[2-(3-trifluoromethylphenyl) ethenyl]-1,3,5-triazine was dissolved in 35 ml pyridine, thereto was added 2.01 g (11.28 mM) nicotinoylchloride hydrochloride, and the mixture was heated under reflux for 4 hours. The reaction liquor was concentrated under reduced pressure, and saturated sodium bicarbonate was added and the mixture was made alkaline, and the precipitated crystals were collected by filtration and washed with water, and thereafter, re-crystallised from ethanol, and the title compound (0.75 g, 43.1 %) was obtained.

Melting point: 127-131°C.

1H-NMR (200 MHz) δ (DMSO-d6): 7.21 (1H, d, J = 15.9 Hz), 7.56 (2H, dd, J = 8.1, 4.9 Hz), 7.60-7.80 (2H, m), 7.90-8.10 (2H, m), 7.94 (1H, d, J = 15.9 Hz), 8.29 (2H, br d, J = 8.1 Hz), 8.78 (2H, dd, J = 4.9, 1.7 Hz), 9.08 (2H, d, J = 1.7 Hz).

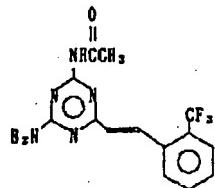
MS m/z (%) [EI]: 491 (M+, 11), 386 (93), 385 (65), 357 (67), 106 (66), 78 (100).

#### Synthesis examples 26-29

The following compounds were synthesised by the same method as in Synthesis Example 25.

**Synthesis example 26**

2-acetylamino-4-amino-[E]-6-[2-(2-trifluoromethylphenyl)ethenyl]-1,3,5-triazine  
(compound 27)  
(0085)



(0086)

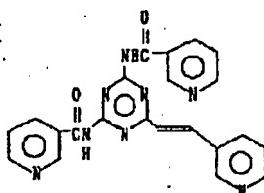
Yield: 54.7 %

Melting point: >300°C (from 2-methoxyethanol).

MS m/z (%) [EI]: 323 (M+, 100), 281 (32), 212 (30), 170 (22).

**Synthesis example 27**

2,4-bis(nicotinoylamino)-[E]-6-[2-(3-pyridyl) ethenyl]-1,3,5-triazine (compound 28)  
(0087)



(0088)

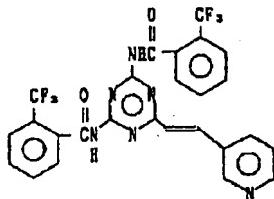
Melting point: 242-247°C (from 2-methoxyethanol).

1H-NMR (200 MHz) δ (DMSO-d6): 7.18 (1H, d, J = 15.9 Hz), 7.48 (1H, dd, J = 8.1, 4.9 Hz), 7.56 (2H, dd, J=8.1, 4.9Hz), 7.91 (1H, d, J=15.9Hz), 8.20 (1H, br d, J = 8.1 Hz), 8.29 (2H, br d, J = 8.1 Hz), 8.60 (1H, br d, J = 4.9Hz), 8.78 (2H, br d, J = 4.9 Hz), 8.85 (1H, brs), 9.08(2H, br s). MS m/z (%) [EI]: 424 (M+, 49), 319(37), 318(100), 106(95), 78 (68).

**Synthesis example 28**

2,4-bis(2-trifluoromethylbenzoylamino)-[E]-6-[2-(3-pyridyl)ethenyl]-1,3,5-triazine

(compound 29)  
(0089)



(0090)

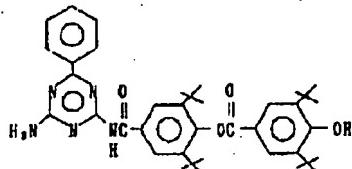
Melting point: 261.7-262.3°C (from ethyl acetate).

1H-NMR (200 MZ) δ (DMSO-d6): 6.83 (1H, d, J=16.1Hz), 7.03 (1H, d, J = 16.1 Hz), 7.45 (1H, dd, J = 8.1, 4.4 Hz), 7.60-7.90 (8H, m), 8.01 (1H, br d, J=8.1Hz), 8.58 (1H, br d, J = 4.4 Hz), 8.64 (1H, br s). MS m/z (%) [EI]: 558 (M<sup>+</sup>, 11), 489(35), 461(43), 433 (21), 173(100), 145(69).

#### Synthesis example 29

2-amino-4-{3,5-di-t-butyl-4-(3,5-di-t-butyl-4-hydroxybenzoyloxy)benzoylamino}-6-phenyl-1,3,5-triazine (compound 43)

(0091)



(0092)

Yield: 28.0 %

Melting point: 167-170°C (from ethyl acetate).

1H-NMR (200 MZ) δ (DMSO-d6): 1.32 (18H, s), 1.44 (18H, s), 7.30-7.60 (6H, m), 7.89 (2H, s), 7.99 (2H, s), 8.24-8.32 (2H, m).

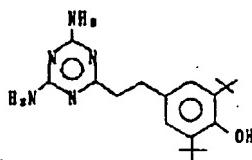
MS m/z (%) [+FAB]: 652.4 (M<sup>+</sup>+1), 233.2.

[+FAB]: 650.3 (M<sup>+</sup>+1), 418.2

#### Synthesis Example 30

2,4-diamino-6-[2-(3,5-di-t-butyl-4-hydroxyphenyl)ethyl]-1,3,5-triazine (compound 50)

(0093)



(0094)

2,4-diamino-[E]-6-{2-(3,5-di-t-butyl-4-hydroxyphenyl)ethenyl}-1,3,5-triazine (compound 37) 0.30 g (0.89 mM) was dissolved in a mixed liquid of 10 ml ethanol and 5 ml ethyl acetate, thereto was added 40 mg 5% Pd/C, and the mixture was stirred at room temperature for 168 hours at normal pressure to hydrogenate. The catalyst was removed by filtration and solvent was distilled off under reduced pressure, and thereafter, the residue was re-crystallised from ethylacetate, to obtain the title compound (0.20 g, 66.6 %).

Melting point: 205.1-206.4°C.

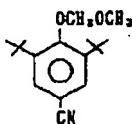
<sup>1</sup>H-NMR (200 MZ) δ (DMSO-d<sub>6</sub>): 1.35 (18H, s), 2.45-2.60 (2H, m), 2.75-2.85 (2H, m), 6.55 (4H, br s), 6.64 (1H, s), 6.88 (2H, s).

MS m/z (%) [EI]: 343 (M+, 92), 328(64), 272(65), 219(54), 126(44), 125(100).

### Synthesis Example 31

(1) 3,5-di-t-butyl-4-methoxymethoxybenzonitrile

(0095)



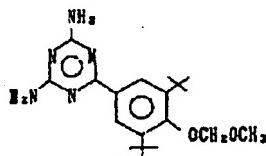
(0096)

3,5-di-t-butyl-4-hydroxybenzonitrile 1.9 g (8.2 mM) was dissolved in 8 ml N,N-dimethylformamide, thereto was added 4.7 ml (29 mM) N-ethyldiisopropylamine, and the mixture was cooled. Methoxymethyl chloride (80%) 2.3 ml (21.4 mM) was added dropwise while cooling with ice and stirring, and thereafter, it was stirred at room temperature for 21 hours. Water was added, and extraction with ethyl acetate was performed, and after washing with water, it was dried with anhydrous sodium sulphate. The solvent was distilled off under reduced pressure, and the residue was purified by silica gel flash chromatography (hexane:ethyl acetate 40:1), to obtain the title compound as a yellow solid (1.43 g, 63.6 %).

(0097)

MS m/z: 276, 275 (M-), 230, 228, 188, 172, 45.

(2) 2,4-diamino-6-(3,5-di-t-butyl-4-methoxyphenyl)-1,3,5-triazine (compound 5)  
(0098)



(0099)

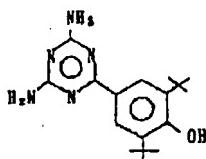
3,5-di-t-butyl-4-methoxybenzonitrile 1.41 g (5.1 mM) was dissolved in 8 ml 2-methoxyethanol, thereto were added dicyanodiamide (90%) and potassium hydroxide (85%) 0.40 g (6.1 mM), and the mixture was heated under reflux for 20 hours. After cooling, water was added, and the precipitated crystals were collected by filtration and washed with water, to obtain the title compound (1.5 g, 82.0 %).

1H-NMR (DMSO-d6) δ: 1.44 (18H, s), 3.57 (3H, s), 4.89 (2H, s), 6.65 (4H, br s), 8.23 (2H, s).

### Synthesis example 32

2,4-diamino-6-(3,5-di-t-butyl-4-hydroxy)phenyl-1,3,5-triazine (compound 38)

(0100)



(0101)

Compound (5) obtained in Synthesis Example 31 (2) 1.45 g (4 mM) was dissolved in a mixture of 50 ml ethanol and 10 ml methanol, thereto was added 1.52 g (8 mM) p-toluene sulphonic acid monohydrate, and the mixture was heated under reflux for 1.5 hours. The reaction liquor was concentrated under reduced pressure, and saturated sodium bicarbonate was added to make it alkaline, and the precipitated crystals were collected by filtration and washed with water, to obtain the title compound (1.12 g, 89.0 %).

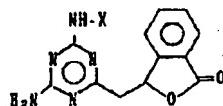
Melting point: >300°C.

1H-NMR (200 MZ) δ (DMSO-d6): 1.43 (18H, s), 6.54 (4H, br s), 7.27 (1H, s), 8.12 (2H, s).

MS m/z (%) [EI]: 315 (M+, 48), 301(21), 300(100), 244(11).

### Synthesis example 33

2,4-diamino-6-phthalidylmethyl-1,3,5-triazine (compound 17)  
(0102)



(0103)

2,4-diamino-6-methyl-1,3,5-triazine 0.5 g (4 mM) was dissolved in 2.5 ml methane sulphonic acid, thereto was added 0.6 g (4 mM) 2-formylbenzoic acid, and the mixture was stirred at 110 °C for 3 hours. After cooling, dilute sodium hydroxide was added to make it alkaline, and the precipitated crystals were collected by filtration and washed with water, and thereafter, re-crystallised from ethanol, to obtain the title compound (0.10 g, 9.8 %). Melting point: 257.0-258.0°C (decomposition) (from ethanol).

1H-NMR (200 MHz) δ (DMSO-d<sub>6</sub>): 2.71 (1H, dd, J=8.8Hz), 3.12 (1H, dd, J=15.1, 4.9Hz), 6.10 (1H, dd, J=8.8, 4.9Hz), 6.72 (4H, br s), 7.60-7.90 (4H, m).

MS m/z (%) [EI]: 258(17), 257 (M+, 100), 229(59), 212(58), 152(59), 133(92), 105(55), 77(62).

(0104)

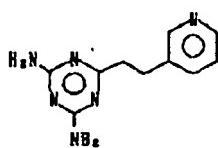
**Example 1**

The following tests were performed using the new compounds obtained in the aforesaid synthesis examples, and 2,4-diamino-[E]-6-{2-(3-pyridyl)ethenyl}-1,3,5-triazine (the compound of Example 1 of Kokai 2-223566) (compound 1), 2,4-diamino-[E]-6-{2-(2,4-dichlorophenyl)ethenyl}-1,3,5-triazine (the compound of Reference Example of Kokai 2-223566) (compound 7), 2,4-diamino-[E]-6-{2-(3-trifluoromethylphenyl)ethenyl}-1,3,5-triazine maleate (the compound of Example 9 of Kokai 2-223566) (compound 11), 2,4-diamino-[E]-6-styryl-1,3,5-triazine [J. Org. Chem., 27, 1717 (1962)] (compound 31), and 2,4-diamino-[E]-6-{2-(4-chlorophenyl)ethenyl}-1,3,5-triazine [J. Org. Chem., 27, 1717 (1962)] (compound 39), and the results are shown in Table 1.

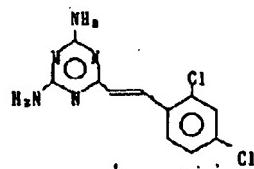
(0105)

Here, for reference, the structural formulae of the aforesaid known compounds is shown below.

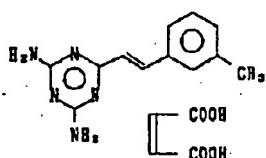
(0106)



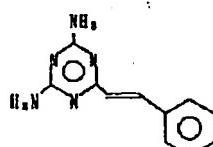
Compound 1



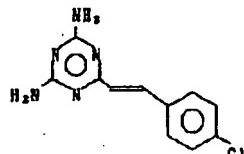
Compound 7



Compound 11



Compound 31



Compound 39

(0107)

Leukotriene C<sub>4</sub> antagonism test

Reagent: Leukotriene C<sub>4</sub> (Wako Pure Chemical Industries)

Histamine dihydrochloride (Wako Pure Chemical Industries)

Test animals: The gastric fundus of SD male rats with bodyweight about 250g (Nippon Charles River) was used.

Nutrient solution: Tyrode solution

NaCl 137.9 mM, KCl 2.7 mM, MgCl<sub>2</sub>.6H<sub>2</sub>O 0.5 mM, NaH<sub>2</sub>PO<sub>4</sub>.2H<sub>2</sub>O 1.1 mM, CaCl<sub>2</sub>.2H<sub>2</sub>O 1.8 mM, NaHCO<sub>3</sub> 11.9 mM, glucose 5.6 mM.

Production of rat gastric fundus samples: Immediately after sacrificing the SD rat by striking the back of the head and exsanguinating, laparotomy was performed and the lower part of the oesophagus and the upper part of the duodenum were each cut with scissors and it was removed, and immersed immediately in prepared nutrient solution. The front of the stomach was cut free and cut open vertically along a small curve, and scissor holes were introduced into the gastric fundus muscle pieces alternately at 3mm width, and this was cut further into lengths of 3 mm.

Magnus apparatus and measurement: Sample was suspended in a Magnus tube containing 20 ml of tyrode solution, and a 1 g load was applied, and a set isotonic contraction was observed in acetylcholine 10<sup>-5</sup>M, it was washed, and after about 20 minutes, the isotonic

contraction (A) of leukotriene C<sub>4</sub> 10<sup>-8</sup>M was recorded as control (100%) contraction. Moreover, it was washed after about 30 minutes, test material was added, and after 10 minutes, leukotriene C<sub>4</sub> 10<sup>-8</sup>M was added and its isotonic contraction (B) was recorded.

Determination of activity:

$$\text{Inhibition rate (\%)} = (1-B/A) \times 100$$

Leukotriene D<sub>4</sub> antagonism test

Reagent: Leukotriene D<sub>4</sub> (Wako Pure Chemical Industries)

Histamine dihydrochloride (Wako Pure Chemical Industries)

Test animal: The ileum of Hartley male guinea pigs with bodyweight about 300g (Kiwa animal) was used.

Nutrient solution: Tyrode solution

NaCl 137.9 mM, KCl 2.7 mM, MgCl<sub>2</sub>.6H<sub>2</sub>O 0.5 mM, NaH<sub>2</sub>PO<sub>4</sub>.2H<sub>2</sub>O 1.1 mM, CaCl<sub>2</sub>.2H<sub>2</sub>O 1.8 mM, NaHCO<sub>3</sub> 11.9 mM, glucose 5.6 mM.

Extraction of guinea pig ileum: The guinea pigs were exsanguinated, the belly was opened and the ileum removed, and the contents were washed and removed from 10 cm near the caecum, and suspended as a tubular sample of about 2 cm in a magnus tube containing tyrode nutrient liquid at 32 °C with 95% O<sub>2</sub> 5% CO<sub>2</sub> flowing through, and a 1 g load was applied.

Magnus apparatus and measurement: After suspending the extracted sample, about 20 minutes and the Magnus tube was filled with nutrient liquid 20 ml at 32 °C with 95% O<sub>2</sub> 5% CO<sub>2</sub> flowing through. A measurement record was observed of isotonic contraction in histamine solution 10<sup>-5</sup>M two times per set, it was washed, and after a further 20 minutes, as a control contraction, isotonic contraction (A) of leukotriene D<sub>4</sub> 10<sup>-8</sup>M was recorded. Furthermore, about 30 minutes after washing, test material was added, and after 10 minutes, leukotriene D<sub>4</sub> 10<sup>-8</sup>M was added and its isotonic contraction (B) was recorded.

Determination of activity:

$$\text{Inhibition rate (\%)} = (1-B/A) \times 100$$

5-Lipoxygenase inhibition test

RBL1 cultured cells were suspended in 50 mM phosphate buffer (pH7.4) containing 10% ethylene glycol and 1 mM ethylene diamine tetraacetic acid (EDTA), so as to have 5 x 10<sup>6</sup> cells/ml, and subjected to ultrasound, then centrifugally separated at 10,000 x G for 10 minutes and 105,000 x G for 60 minutes, and the supernatant was taken as the 5-lipoxygenase enzyme sample.

**(0108)**

10 µM arachidonic acid as substrate, the enzyme sample obtained as above, and a DMSO solution of the compound obtained in specific examples, made to have final concentration 10 µM, were taken into a test tube and made to react for 10 minutes at 37 °C. Butyl 3,5-dinitrobenzoate 10 µl of 0.25M was added as an internal standard, and extraction with 1.8 ml of hexane was performed. The quantity of 5-HETE in this was measured by high-performance liquid chromatography [column, TSKgel ODS-80TM (TOYO SODA) with mobile phase of acetonitrile: water: ethyl acetate = 60:40:0.02, flow rate 1 ml/min, detection, UV (235 nm)].

**(0109)**

From the results, the 5-lipoxygenase inhibition rate was calculated according to the following formula

$$\text{Inhibition rate} = \{(C-S)/C\} \times 100 (\%)$$

C: 5-HETE peak area when compound obtained in specific examples was not included (corrected using internal standard)

C: 5-HETE peak area when compound obtained in specific examples was included (corrected using internal standard)

(0110)

Table 1

Compound Number	leukotriene antagonism (%)			5-lipoxygenase inhibition (%) 10µM
	C <sub>10</sub> 10 µM	D <sub>4</sub> 100 µM	D <sub>4</sub> 10 µM	
1	60			
7	76			
11	75			
19	49	18		
20	88		36	
21	69		6	
22	25	30		
23		59		
31	53			
32		57		
33	55	72		
34	76		88	
35	38		19	
36	42			
37		100	82	100
38		82		68
39		45		
41		99		
42		38		
43				46
45		28		
46		100		
47			88	
48		69		
49		84		48
50				63

(0111)

**Preparation Example 1**Tablet preparation

(1)	2,4-diamino-[E]-6-(2-(3,5-di-t-butyl-4-hydroxyphenyl)ethenyl)-1,3,5-triazine	10 g
(2)	lactose	90 g
(3)	corn starch	29 g
(4)	magnesium stearate	1 g
	1000 tablets	130 g

(1), (2) and 17 g of corn starch were mixed, and granulated with a paste made from 7g of corn starch. To the granulate was added 5 g of corn starch and (4), and the mixture was compressed in a tabletting machine to form 1000 tablets containing 10 mg of (1) per tablet.

**Preparation Example 2**

Capsule preparation

(1)	2,4-diamino-[E]-6-{2-(4-hydroxy-3,5-dimethylphenyl)ethenyl}-1,3,5-triazine	200 g
(2)	lactose	150 g
(3)	corn starch	100 g
(4)	crystalline cellulose	40 g
(5)	light silica	5 g
(6)	magnesium stearate	5 g
	1000 tablets	500 g

In accordance with the usual way, each of the aforesaid components was mixed and the material as a granulate was filled into 1000 capsules, to produce capsules each containing 500 mg.

**Test Example 1**

Acute toxicity test

Cases of death were not observed when the compounds of Synthesis Example 1-33 and the known compounds used in Example 1 were administered orally to ddY mice (each amount used, 10 animals per group), even when the amount administered was up to 1000 mg/kg, and it was confirmed that the effective component of the leukotriene antagonist of this invention had low acute toxicity and high safety.

(0112)

Effect of the Invention

In accordance with this invention, leukotriene antagonists can be provided having 2,4-diamino-1,3,5-triazine derivatives as effective component.

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